UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
ADDRESS: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/462,846	01/13/2000	DAVID A. ESTELL	GC381-US	5580

5100 7590 12/19/2002

GENENCOR INTERNATIONAL, INC.
925 PAGE MILL ROAD
PALO ALTO, CA 94304

EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	22

DATE MAILED: 12/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/462,846	ESTELL, DAVID A.
Examiner	**Art Unit**
David J. Steadman	1652

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-13,15 and 20-23* is/are pending in the application.

4a) Of the above claim(s) *2,3,10-12,22 and 23* is/are withdrawn from consideration.

5)☒ Claim(s) *1* is/are allowed.

6)☒ Claim(s) *6-9,13,15,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Application Status

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 15 November 2002 has been entered.

Claims 1-3, 6-13, 15, and 20-23 are pending in the application.

Applicants' amendment to claims 1, 6, 13, and 20, addition of claims 22 and 23, and cancellation of claims 4, 5, 14, and 16-19 in Paper No. 21, filed 11/15/02, is acknowledged.

Claims 2, 3, 10-12, 22, and 23 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 1, 6-9, 13, 15, 20, and 21 are being examined on the merits.

It is noted that applicants have presented arguments to an objection and a rejection that were previously withdrawn in Paper No. 18 (see below for details). Applicants' arguments filed in Paper No. 21 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "*Bacillus subtilis* With An Inactivated Cysteine Protease-1". See MPEP § 606.01 regarding examiner's change in title.

Claim Objections

2. Applicants present an argument addressing an objection to the term "wpr". This objection was previously withdrawn (see item 7 of Paper No. 18) and therefore, a response by the examiner is not required.

3. Claim 9 is objected to because of the following informalities: the term "mutases transferases" is grammatically incorrect and should be replaced with, for example, "mutases, transferases". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

4. Claims 6-9, 13, 15, 20, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 6-9 recites the limitation "said microorganism" in claim 6 and "The microorganism" in claims 7-9. There is insufficient antecedent basis for these limitations in the claims. In order to correct antecedent basis, it is suggested that applicants replace the term "said microorganism" in claim 6 with "said *Bacillus subtilis*", and replace the term "The microorganism" in claims 7-9 with "The *Bacillus subtilis*".

b. Claims 13 (claims 20 and 21 dependent therefrom) and 15 are unclear as the preamble of claim 13 recites "a method for the production of a heterologous protein in a transformed *Bacillus subtilis* host cell", however, the method steps are limited only to a "*Bacillus* host cell" and not to a "*Bacillus subtilis* host cell". Due to the inconsistent use of terms, it is unclear as to the scope of host cells used in the methods. In order to clarify the meaning of the claims, it is suggested that applicants replace "*Bacillus*" in lines 3 and 8 of claim 13 and line 1 of claim 15 with "*B. subtilis*".

c. Claims 13 (claim 15 dependent therefrom) and 20 (claim 21 dependent therefrom) are confusing in the recitation of "at least one of the genes encoding *B. subtilis* cysteine protease 1,

wherein said at least one of the genes" in claim 13 and "at least one of the genes encoding cysteine protease 1" in claim 20. The claims are confusing as it appears from the claims that *Bacillus subtilis* comprises multiple genes encoding the cysteine protease-1 of SEQ ID NO:2. However, there is no indication in the specification and the prior art that *B. subtilis* comprises a plurality of genes encoding the protein of SEQ ID NO:2. It is suggested that applicants clarify the meaning of the claim by replacing the term "at least one of the genes encoding *B. subtilis*" with, for example, "a gene encoding *B. subtilis* cysteine protease 1, wherein said gene" in claim 13 and replacing the term "at least one of the genes encoding cysteine protease 1" in claim 20, with for example, "gene encoding cysteine protease 1" in claim 20.

Claim Rejections - 35 USC § 112, First Paragraph

5. Claims 13, 15, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13 and 20 are drawn to a method for the production of a heterologous protein in a transformed *B. subtilis* host cell using a *B. subtilis* host cell comprising a genus of genes encoding SEQ ID NO:2 (claim 13) or the nucleic acid of SEQ ID NO:1 (claim 20) with any mutation. Claims 15 and 21 are drawn to the methods of claims 13 and 20, respectively, wherein the *B. subtilis* host cell further comprises a genus of mutant genes encoding a protease selected from apr, npr, epr, wpr, and/or mpr protease. The claims are rejected because the function of the mutant genes has not been adequately described in the specification. While it is acknowledged that the instant claims are drawn to methods of using *B. subtilis* host cells comprising said mutant genes and not the mutant genes themselves, said mutant genes are an essential element of the claimed invention and thus should be adequately described in the specification. The specification does not contain any disclosure of the function of all mutant nucleic acids as encompassed by the recited genera. The genera of nucleic acids that comprise the mutant genes

as described above is a large variable genus with the potentiality of encoding many different proteins having distinct functions. Therefore, many functionally unrelated nucleic acids are encompassed within the scope of these claims. The specification discloses only a single representative species of such mutants of a gene encoding SEQ ID NO:2 or a mutant SEQ ID NO:1, i.e., a gene encoding SEQ ID NO:2 or the nucleic acid of SEQ ID NO:1 with a mutation that inactivates CP1 proteolytic activity. In an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus. Furthermore, the specification does not teach any representative species of mutant genes encoding a protease selected from apr, npr, epr, wpr, and/or mpr protease. This description is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genera of nucleic acids. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

6. Claims 13, 15, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of a heterologous protein in a transformed *B. subtilis* host cell using a *B. subtilis* host cell comprising a gene encoding SEQ ID NO:2 or the nucleic acid of SEQ ID NO:1 with a mutation or deletion that results in the inactivation of CP1 activity, does not reasonably provide enablement for a method for the production of a heterologous protein in a transformed *B. subtilis* host cell using a *B. subtilis* host cell comprising a gene encoding SEQ ID NO:2 (claim 13) or the nucleic acid of SEQ ID NO:1 (claim 20) with *any* mutation and optionally wherein the *B. subtilis* host cell further comprises *any* mutation in a gene encoding a protease selected from apr, npr, epr, wpr, and/or mpr protease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Undue experimentation would be required for a skilled artisan to make and use the invention as broadly claimed. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the

quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 13, 15, 20, and 21 are so broad as to encompass a method for the production of a heterologous protein in a transformed *B. subtilis* host cell using a *B. subtilis* host cell comprising any mutant genes encoding proteins having any activity as described above. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant genes broadly encompassed by the claims. Since the nucleotide sequence of an encoding nucleic acid determines a protein's structural and functional properties, predictability of which changes in the nucleotide sequence can be tolerated and obtain a polypeptide having the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method for the production of a heterologous protein in a transformed *B. subtilis* host cell using a *B. subtilis* host cell comprising a gene encoding SEQ ID NO:2 or the nucleic acid of SEQ ID NO:1 with a mutation or deletion that results in the inactivation of CP1 activity.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within an encoded protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. The prior art teaches that modifications to an encoding nucleic acid, even minor modifications, may completely alter the function of the encoded protein sequence. As a representative example, Broun et al. (*Science* 282:1315-1317, 1998) teach that as few as four amino acid

substitutions in a polypeptide having approximately 380 amino acids completely alters the enzymatic function of the polypeptide from a desaturase to a hydroxylase (see abstract). Thus, without sufficient guidance, there is a high degree of unpredictability in mutating an encoding nucleic acid with an expectation of obtaining a polypeptide having the desired function.

The specification does not support the broad scope of the claims which encompass a method for the production of a heterologous protein in a transformed *B. subtilis* host cell using a *B. subtilis* host cell comprising genes with any mutations encoding proteins having any activity as described above because the specification does not establish: (A) regions of the encoded protein structure which may be modified with the expectation of obtaining a *B. subtilis* host cell with the desired biological characteristics; (B) the general tolerance of a *B. subtilis* host cell to any mutation within a gene encoding SEQ ID NO:2, the gene of SEQ ID NO:1, or the recited proteases; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible mutations within the recited genes is likely to provide the desired result.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method for the production of a heterologous protein in a transformed *B. subtilis* host cell using a *B. subtilis* host cell comprising genes with any mutations encoding proteins having any activity as described above. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The examiner has attempted to address applicants' arguments to the extent the arguments pertain to the instant rejection. Applicants argue any mutation or deletion that results in the inactivation of CP1 activity is intended or in combination with mutations or deletions of the recited protease genes. Applicants argue they are not required to disclose each mutation or deletion that would result in CP1

inactivation. Applicants argue the specification discloses methods for identifying CP1 nucleic acids and polypeptides and to assess CP1 proteolytic activity and the genes encoding the recited proteases are known in the art. It is noted that the claims are not so limited to a mutation of a gene encoding SEQ ID NO:2 or the nucleic acid of SEQ ID NO:1 that results in inactivation of CP1 proteolytic activity. As written, the mutation of a gene encoding SEQ ID NO:2, the nucleic acid of SEQ ID NO:1, or genes encoding the recited proteases can result in proteins having any amino acid sequence and any function or nucleic acids encoding said proteins. As described above, undue experimentation would be required for a skilled to make and the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 102

7. It is noted that applicants present arguments addressing the rejection of claims 1, 4-9, and 13-17 under 35 USC 102(b) as being anticipated by WO 89/10976. This rejection was previously withdrawn for the reasons discussed in item 12 of Paper No. 18. Therefore, a response to this rejection is not required.

8. Claims 13, 15, 20, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferrari et al. (US Patent 5,264,366; hereafter referred to as "Ferrari"). Claims 13 and 20 are drawn to a method for the production of a heterologous protein in a transformed *B. subtilis* host cell comprising the steps of: obtaining a *B. subtilis* host cell comprising a nucleic acid encoding a heterologous protein and containing a mutation or deletion in a gene encoding SEQ ID NO:2 or the nucleic acid of SEQ ID NO:1 and growing the *B. subtilis* host cell under conditions suitable for the expression of said heterologous protein. Claims 15 and 21 limit the host cell of the methods of claims 13 and 20, respectively to a cell that further comprises a mutation or deletion in the recited proteases. As the mutant genes of the recited *B. subtilis* host cell can encode any protein, the host cell can essentially be any transformed *B. subtilis* host cell. Therefore, in accordance with MPEP 2111, the claims have been interpreted in their broadest reasonable interpretation as a method of producing a heterologous protein using any transformed *B. subtilis* host cell. Ferrari teaches a method for recombinant expression of a *B. amyloliquefaciens* subtilisin gene in a *B. subtilis* host cell by first transforming a *B. subtilis* with a plasmid comprising a *B. amyloliquefaciens*

subtilisin gene and cultured to express *B. amyloliquefaciens* subtilisin. This anticipates claims 13, 15, 20, and 21 as written.

Conclusion

9. Claim 1 is in a condition for allowance.

10. Claims 6-9, 13, 15, 20, and 21 are rejected.

11. Claims 6-9 would be allowable if rewritten to overcome the objection(s) and/or rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action.

12. Claims 2, 3, 10-12, 22, and 23 are withdrawn from consideration.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652